LETTER

High-density lipoprotein is a nanoparticle, but not all nanoparticles are high-density lipoprotein

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High-density lipoprotein (HDL) is a natural nanoparticle that transports cholesterol from peripheral tissues to the liver and also transports other lipids, proteins, enzymes, and microRNAs. HDL–cholesterol levels are negatively correlated with the risk of cardiovascular events. HDL has also been shown to reduce inflammation and to improve endothelial function (1). Because of HDL's biological importance, its inherent "stealthy" nature and targeting of certain cell types of interest, several groups, including ours, have developed approaches to label HDL with contrast-generating substances or loaded it with drugs, forming "HDL-like" nanoparticles (2).

HDL has certain key features that can be roughly divided into three categories (3). (*i*) HDL's diameter should be in the 7- to 13-nm range, and its density should be between 1.066 and 1.21 g/mL. (*ii*) HDL is composed of a natural phospholipid coating that has the apolipoproteins of HDL embedded, particularly apolipoprotein (apo) A-I, covering a hydrophobic core of predominately cholesteryl esters. (*iii*) HDL has a wide array of biological functions, which include reverse cholesterol transport, anti-inflammatory activity, and specific interactions with several cell surface proteins such as scavenger receptor B1, ATP-binding cassette (ABC)A1, and ABCG1. Synthetic approaches to HDL and inclusion of nonnatural substances to provide additional functionality may compromise some of these properties, such as the density, size, or cholesterol efflux capacity. Nevertheless, if the majority of the characteristics of HDL are met by a certain nanoparticle, it is reasonable to describe it as HDL-like (4).

With these considerations in mind, we read with interest the work by Marrache and Dhar in a recent issue of PNAS (5). In this work, a hydrophobic poly(lactic-*co*-glycolic) acid core nanoparticle is presented as being HDL-like. Its coating consisted of a nonnatural, polyethylene glycol-appended distearoyl phospholipid. With the aim of introducing HDL-like properties, the 4F peptide, which mimics some of the properties of apoA-I, was incubated with the nanoparticles after their synthesis. Other components, such as a stearyl triphenyl phosphonium lipid, cholesterol oleate, and quantum dots, were also included. The overall size of the nanoparticle was found to be 123 nm.

This nanoparticle, which has a diameter 10 times larger than natural HDL and has an unreported density, includes mostly nonnatural substances. In terms of the biological properties, neither cholesterol efflux from macrophage cells nor binding to HDL's natural targets are shown. Despite the use of the 4F apoA-I mimetic peptide, binding to a nonnatural target, mitochondria, is shown, likely because of the cationic lipid used. Potent anti-inflammatory effects were not observed. In this respect, it is interesting to note that the clinical development of the 4F peptide as a candidate apoA-I mimetic has been discontinued.

With the currently reported data, the nanoparticle presented by Marrache and Dhar (5) does not meet any of the aforementioned HDL characteristics and is, therefore, not HDL-like.

1 Navab M, Reddy ST, Van Lenten BJ, Fogelman AM (2011) HDL and cardiovascular disease: Atherogenic and atheroprotective mechanisms. *Nat Rev Cardiol* 8(4):222–232.
2 Skajaa T, et al. (2010) High-density lipoprotein-based contrast agents for multimodal imaging of atherosclerosis. *Arterioscler Thromb Vasc Biol* 30(2):169–176.
3 Mahley RW, Innerarity TL, Rall SC, Jr., Weisgraber KH (1984) Plasma lipoproteins: Apolipoprotein structure and function. *J Lipid Res* 25(12):1277–1294.
4 Skajaa T, et al. (2011) The biological properties of iron oxide core high-density lipoprotein in experimental atherosclerosis. *Biomaterials* 32(1):206–213.
5 Marrache S, Dhar S (2013) Biodegradable synthetic high-density lipoprotein nanoparticles for atherosclerosis. *Proc Natl Acad Sci USA* 110(23):9445–9450.

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Conflict of interest statement: E.A.F. and Z.A.F. hold a patent on HDL nanoparticles as contrast agents.

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